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HEAD AND NECK

Core needle biopsy could reduce diagnostic surgery in patients with anaplastic thyroid cancer or thyroid lymphoma

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Abstract
Objective To evaluate the diagnostic performance of fine needle aspiration (FNA) and core needle biopsy (CNB) in patients with anaplastic thyroid cancer (ATC) or thyroid lymphoma (TL).
Methods Between January 2000 and March 2012, 104 patients were diagnosed with ATC or TL by means of ultrasound (US)-guided FNA, CNB, or surgery. This study ultimately included 99 patients with ATC (n=59) or TL (n=40). We evaluated the sensitivity and positive predictive value of FNA and CNB for the diagnosis of ATC and TL, and compared the rates of diagnostic surgery between FNA and CNB.
Results FNA was used in 83 patients, and CNB was used in 32 patients initially (n=16), after FNA results (n=8), or simultaneously with FNA (n=8). CNB achieved sensitivity of 87.5 % (28/32) and positive predictive value of 100.0 % (28/28) for the diagnosis of ATC and TL. The respective values for FNA were 50.6 % (40/79) and 90.9 % (40/44). The rate of diagnostic surgery was significantly lower after CNB (4/32, 12.5 %) than after FNA (28/79, 35.4 %) (p= 0.020).
Conclusions CNB was able to reduce unnecessary diagnostic surgery in patients with ATC or TL by virtue of its superior diagnostic sensitivity and positive predictive value compared to FNA.
Key points
• *Diagnostic sensitivity and PPV for CNB were 87.5 % and 100.0 %, respectively.*
• *The respective values for FNA were 50.6 % and 91.0 % for ATC and TL.*
• *Diagnostic surgery rates were reduced after CNB compared to FNA (p= 0.020).*

Keywords Anaplastic thyroid cancer · Thyroid lymphoma · Thyroid nodule · Core needle biopsy · Fine needle aspiration

Abbreviations

ATC	Anaplastic thyroid cancer
AUS	Atypia (or follicular lesion) of undetermined significance
CNB	Core needle biopsy
FNA	Fine needle aspiration
TL	Thyroid lymphoma
US	Ultrasonography

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Introduction

Anaplastic thyroid cancer (ATC) and thyroid lymphoma (TL) both present as a rapidly growing thyroid mass in elderly patients. Since they commonly lead to local compressive and invasive symptoms such as neck pain, dysphagia, hoarseness, and dyspnoea, prompt diagnosis and appropriate treatment is necessary for a good prognosis [1–4]. With regard to treatment strategy and prognosis, ATC has a high mortality rate and requires a multimodal treatment approach comprising radiotherapy, chemotherapy, and/or surgery. On the contrary, the prognosis for TL is excellent, with treatment consisting of chemotherapy with or without radiotherapy [4–8]. Since ATC and TL have distinct therapeutic strategies and prognosis, it is important that they are accurately diagnosed and are differentiated from one another and from other types of thyroid cancer [9, 10].

In terms of effective diagnostic strategies, however, fine needle aspiration (FNA) is limited in its ability to provide an accurate diagnosis of ATC or TL. Diagnostic sensitivity as reported in the literature varies widely, from 25 to 90 %, and in a significant percentage of cases, FNA results are suggestive but not diagnostic [8, 11–18]. As a result, patients with clinically suspected ATC or TL commonly undergo FNA followed by diagnostic surgery [19, 20]. As an alternative to FNA, core needle biopsy (CNB) has been suggested to have advantages for the diagnosis of ATC and TL. Diagnostic sensitivity of up to 100 % has been reported, and CNB may obviate the need for diagnostic surgery [21–26]. Although CNB results thus far appear promising, given the small number of cases in previous studies, further research is needed.

The present study was performed to test the hypothesis that CNB would reduce the need for diagnostic surgery in patients with ATC or TL by virtue of its superior diagnostic performance compared to FNA. To test this hypothesis, we calculated the diagnostic performance of FNA and CNB and compared the rates of diagnostic surgery in patients with ATC or TL over a 10-year period at a single institution.

Materials and methods

Patient selection

This retrospective study was approved by our institutional review board, and written informed consent was obtained from all patients before FNA or CNB were performed. We reviewed the medical records and ultrasound (US) images of patients at our institution who were diagnosed with ATC or TL between January 2000 and March 2012. Over this period, 104 patients were initially diagnosed with ATC (n=59) or TL (n=45) using US-guided FNA, US-guided CNB, or surgery. The choice of modality between FNA and CNB was based on clinician preference. Of these 104 patients, five were excluded because FNA or CNB was not performed before surgery. Thus the study ultimately included 99 patients with ATC (n=59) or TL (n=40), the final diagnosis of which was based on surgical (n=61) or clinicopathologic results (n=38). The latter included 19 patients with TL who responded to treatment and 19 patients with ATC for whom surgery was contraindicated and who ultimately died 36 days to 18 months after FNA or CNB diagnosis of ATC.

US-guided FNA and CNB procedures

US examinations were performed using one of three US systems—an iU22 unit (Philips Healthcare, Andover, MA, USA), an EUB-7500 unit (Hitachi Medical Corporation, Tokyo, Japan), or an HDI 5000 (Philips Healthcare)—all of which were equipped with a high-frequency linear probe (5–14 MHz). All US examinations and US-guided FNAs or CNBs were performed by experienced staff or fellow radiologists with 5–17 years of clinical experience in performing and evaluating thyroid US images. US-guided FNAs were performed with 23-gauge needles and a combination of capillary and aspiration FNA techniques, according to the characteristics of the nodules. Each lesion was aspirated at least twice (range 2–4 times). Material obtained from the FNA was immediately placed in 95 % alcohol for Papanicolaou staining. US-guided CNBs were performed using a disposable 18-gauge double-action spring-activated needle (1.1-cm or 1.6-cm excursion; TSK Acecut; TSK Laboratory, Tochigi-Ken, Japan) after local anaesthesia with 1 % lidocaine. Using a freehand technique, the core needle was advanced from the isthmus of the thyroid toward the target nodule using the trans-isthmic approach. When the needle tip was advanced into the edge of the nodule, the stylet and cutting cannula of the needle were sequentially fired with careful consideration. The number of tissue cores obtained by CNB ranged from one to three. A second or third CNB was performed when the lesion was considered inaccurately targeted, in the case of small nodules, or when an adequate tissue core was not obtained, based on visual inspection. Each patient was observed after firm, local compression of the biopsy site for 10–30 minutes after FNA or CNB.

Cytology and histopathology analysis

FNA, CNB, and surgical specimens were reviewed by cytopathologists with 8–10 years of clinical experience in thyroid cytopathology. FNA cytology diagnoses were categorized based on the Bethesda system: non-diagnostic, benign, atypia of undetermined significance (AUS), follicular neoplasm, suspicious for or definite diagnosis of ATC, suspicious for or definite diagnosis of TL, or other type of malignancy. Given that the diagnostic criteria for CNB of thyroid nodules have not been standardized, CNB findings were classified into categories similar to those used in the analysis of FNA cytology. Additional special staining on FNA or CNB specimens was not routinely used for these readings, but could be used as an additional requirement of the cytopathologists to obtain a confirmative diagnosis. It was performed on a case-by-case basis at the cytopathologists' discretion.

Statistical analyses

Statistical analyses were performed using the MedCalc for Windows software package, version 10.2 (MedCalc Software, Ostend, Belgium). We evaluated the rates for each diagnostic category, and calculated the diagnostic sensitivity and positive predictive value of FNA and CNB for the diagnosis of ATC and TL. All diagnoses were made with FNA or CNB specimens for thyroid nodules. Diagnostic surgery was defined as that performed when the nodule was initially misdiagnosed as non-ATC or non-TL, but was confirmed as ATC or TL on subsequent surgery performed for a diagnostic purpose. The rates of diagnostic surgery were compared between patients who underwent FNA and CNB. Chi-square and Mann–Whitney *U* tests were used to evaluate relationships in demographic characteristics between patients with ATC and TL, and the Fisher's exact test was used to compare the sensitivity and positive predictive value between FNA and CNB for the diagnosis of ATC or TL. A p value<0.05 was considered statistically significant.

Results

Demographic data

Figure 1 shows the inclusion criteria and diagnostic approach among patients. Of the 59 ATCs and 40 TLs, FNA was initially applied for 83 masses, and CNB was used for 32 masses initially (n=16), after FNA results (n=8), or simultaneously with FNA (n=8). The demographic data of patients included in this study are presented in Table 1. Patients with ATC were significantly older than patients with TL (p<0.001). There was no significant difference in gender between the ATC and TL groups (p=0.125). Almost all patients with ATC presented with a rapidly growing thyroid mass at initial diagnosis, while TL was detected in some patients incidentally (p= 0.007). Sixteen of 40 patients with TL and 38 of 59 patients with ATC had significant lymphadenopathy with thyroid masses.

With regard to the hormonal and autoantibody status of the patients, 24 of 30 (80.0 %) patients with TL and 14 of 46 (30.4 %) with ATC displayed elevated levels of thyroid autoantibodies. Among them, 9 of 40 (22.5 %) patients with TL had a history of Hashimoto's thyroiditis, whereas no patient with ATC had such history (p<0.001).

Diagnostic value of US-guided FNA and CNB

Table 2 shows data reflecting the comparison between the initial FNA and CNB results and the final diagnosis in patients with ATC and TL. For ATC, the diagnostic sensitivity and positive predictive value with FNA were 54.0 % (27/50; 95 % CI: 39.3, 68.2) and 87.1 % (27/31; 95 % CI: 70.2, 96.3), respectively, improving to 76.9 % (10/13; 95 % CI: 46.2, 94.7) and 100.0 % (10/10; 95 % CI: 69.0, 100.0), respectively, for CNB. For TL, the diagnostic sensitivity and positive predictive value were 44.8 % (13/29; 95 % CI: 26.5, 64.3) and 100.0 % (13/13; 95 % CI: 75.1, 100.0), respectively, for FNA, and were 94.7 % (18/19; 95 % CI: 73.9, 99.1) and 100.0 % (18/18; 95 % CI: 81.3, 100.0), respectively, for CNB. For combined ATC and TL, diagnostic sensitivity and positive predictive value were 50.6 % (40/79; 95 % CI: 39.1, 62.1) and 90.9 % (40/44; 95 % CI: 78.3, 97.4), respectively, for FNA, improving to 87.5 % (28/32; 95 % CI: 71.0, 96.4) and 100.0 % (28/28; 95 % CI: 87.5, 100.0), respectively, with CNB (p=0.0002, p=0.152). There were no significant complications during or after CNB.

Regarding lymphadenopathy, FNA or CNB were additionally performed for lymphadenopathy in 17 of 99 patients [TL (n=6) and ATC (n=11)]. However, there was no case of additional diagnostic value for ATC or TL in our study.

Diagnostic surgery after FNA and CNB

Table 3 shows the rates of diagnostic surgery in patients with ATC and TL after FNA compared with those after CNB. For ATC, diagnostic surgery was performed in 34.0 % (17/50) of patients after FNA and 23.1 % (3/13) of patients after CNB. CNB resulted in a reduction in diagnostic surgery compared to FNA, but this was not statistically significant (p=0.524). For TL, diagnostic surgery was performed in 37.9 % (11/29) of patients after FNA and 5.3 % (1/19) of patients after CNB. CNB significantly reduced the rate of diagnostic surgery compared to FNA (p=0.016). For ATC and TL combined, diagnostic surgery was performed in 35.4 % (28/79) of patients after FNA, and was significantly decreased, to 12.5 % (4/32), after CNB (p=0.020).

Discussion

The present study demonstrated that 98.3 % (58/59) of ATC and 82.5 % (33/40) of TL presented as a rapidly growing neck mass. CNB achieved diagnostic sensitivity of 87.5 % and positive predictive value of 100.0 %, while the respective values for FNA were 50.6 and 90.9 %, suggesting that CNB

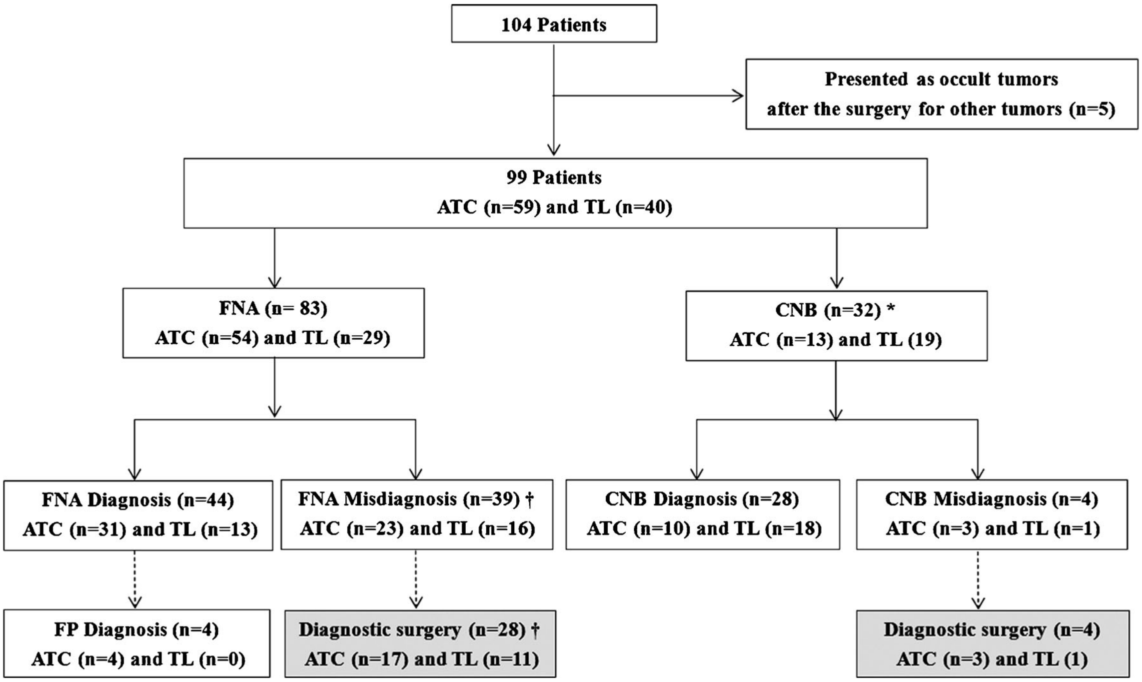

Fig. 1 Inclusion criteria and diagnostic approach for patients in this study. *Note:* Data indicate number of patients. *ATC* anaplastic thyroid cancer, *CNB* core needle biopsy, *FNA* fine needle aspiration, *FP* false positive, *TL* thyroid lymphoma *CNB was performed initially (n=16), after FNA (n=8), or simultaneously with FNA (n=8). †Two patients with TL were initially misdiagnosed with ATC after FNA, but TL was ultimately confirmed with diagnostic surgery.

is a superior diagnostic tool for ATC and TL compared to FNA. Based on this performance, CNB was successful in reducing the rate of diagnostic surgery in patients with ATC or TL.

With regard to the results of FNA for the diagnosis of ATC or TL, diagnostic sensitivity reported in the literature has varies widely, from 25 to 90 % [8, 11–18]. Based on these data, diagnostic surgery has been strongly recommended when ATL or TL are suspected clinically or on FNA [19, 20]. CNB studies, however, have shown higher sensitivity, ranging from 80 to 100 %, and in most cases were diagnostic [21–28]. As such, several investigators have emphasized the importance of CNB in avoiding unnecessary diagnostic surgery, although the number of patients in their studies was small, with ten at the maximum. In our study, we demonstrated the higher sensitivity of CNB compared to FNA (87.5 % versus 50.6 %, respectively; p=0.0002), and evaluated the diagnostic performance of FNA and CNB for a larger patient population. CNB improved sensitivity by reducing non-diagnostic, benign, and AUS results, and improved positive predictive value as well by preventing false-positive diagnoses. There were no patients with lesions misdiagnosed as benign with CNB, while there were 11 such patients (13.3 %) with FNA.

Although diagnostic surgery allows a definitive diagnosis, it may increase morbidity and mortality in elderly patients and can delay proper management in patients with ATC or TL. Even from a therapeutic point of view, this surgery is unnecessary in patients with TL, and should be restricted to resectable tumours in patients with ATC [5–8]. Thus surgery should be applied only in select patients. In this study, we considered patients with ATC or TL together, since they present in a similar clinical setting—a rapidly growing thyroid mass in elderly patients—and because ATC and TL can be confused in clinical and cytological aspects. In addition, US features may not be helpful for differentiating TL from chronic thyroiditis and ATC from other high-grade carcinoma. In our study, we also found that TL and ATC could not be reliably differentiated on US. Since ATC and TL usually presented as a diffuse infiltrative pattern, differentiation between them was

Table 1 Demographic data of patients with anaplastic thyroid cancer (ATC) or thyroid lymphoma (TL)

	ATC (n=59)	TL (n=40)
Age (mean±standard deviation)	67.0±13.0	59.0±13.6
Age (range)	20–91	30–90
Sex (female : male)	49:10	28:12
Rapidly growing tumor	58	33
Previous history of HT*	0/59	9/40
Increased serum TSH*	5/52	17/36
Thyroid autoantibody (+)*	14/46	24/30

ATC anaplastic thyroid cancer, *HT* Hashimoto's thyroiditis, *TL* thyroid lymphoma, *TSH* thyroid-stimulating hormone

* Data indicate the ratio of each patient among the confirmed patients.

Table 2 Comparison of initial FNA and CNB results with the final diagnosis in patients with ATC or TL

Final diagnosis	Initial FNA results (n=83)							CNB (n=32)*			
	ND	Benign	AUS	Follicular neoplasm	ATC	TL	Malignancy, other	AUS	ATC	TL	Malignancy, other
ATC	1	5	4	1	27	-	12†	-	10	-	3†
TL	1	6	5	-	2	13	2‡	1	-	18	-
PTC	-	-	-	-	1	-	-	-	-	-	-
Metastasis	-	-	-	-	3		-	-	-	-	-

Note: Data indicate the number of nodules.

ATC anaplastic thyroid carcinoma, *AUS* atypia (or follicular lesion) of undetermined significance, *CNB* core needle biopsy, *FNA* fine needle aspiration, *ND* non-diagnostic, *PTC* papillary thyroid carcinoma, *TL* thyroid lymphoma

* CNB was performed initially (n=16), after FNA results of non-ATC or non-TL (n=8), or simultaneously with FNA (n=8).

† Other types of malignancy initially diagnosed by FNA in patients with ATC included PTC (n=7), malignancy of uncertain type (n=2), fibrohistiocytic neoplasm (n=1), and high-grade carcinoma (n=2). Those diagnosed by CNB included PTC (n=1), malignancy of uncertain type (n=1), and high-grade carcinoma (n=1).

‡ Other types of malignancy after FNA in patients with TL included round cell malignant neoplasm (n=1), and high-grade carcinoma (n=1).

difficult, consistent with previous reports in the literature [10, 29]. However, as treatment strategy and prognosis are entirely different between the two diseases, both should be considered concurrently in determining the initial diagnostic procedure, and they must be differentiated after the procedure. In our study, the superior diagnostic performance of CNB enabled a significant reduction in diagnostic surgery, from 35.4 to 12.5 %, in patients with ATC or TL (p=0.020).

Recent studies have demonstrated that advances in ancillary techniques such as flow cytometry can improve the diagnostic sensitivity of FNA for TL. Investigators therefore could employ flow cytometry using the FNA aspirates in clinical settings consistent with TL: patients with a rapidly growing goiter who have a long-standing history of Hashimoto's thyroiditis. The application of flow cytometry to FNA aspirates without obvious clinical information, however, may be limited. Previous studies have reported that 49.6–57.7 % of patients with TL presented with a history of Hashimoto's thyroiditis [30, 31], and this proportion was estimated at 22.5 % in our study. Inadequate sampling may remain a limitation for the use of flow cytometry in the diagnosis of TL [32, 33]. As CNB in our study showed 94.7 % sensitivity for TL in the absence of non-diagnostic results, this approach may help to ensure accurate diagnosis, and could represent an attractive alternative in patients with a rapidly growing thyroid mass, regardless of a history of Hashimoto's thyroiditis. Moreover, biopsy of the thyroid mass was sufficient for diagnosis even in patients with additional lymphadenopathy.

Our study has several limitations. First, it was retrospective in nature and may have had selection bias. However, as the low incidence of ATC and TL limits the feasibility of a prospective design, this may be the best modality for retrospectively reviewing clinical experience over extended periods. Second, flow cytometry using the FNA aspirates was not applied in our study. Further studies are needed to compare diagnostic value between CNB and flow cytometry using FNA aspirates, and to evaluate the role of flow cytometry using CNB specimens as well. Third, the lack of diagnostic category standardization in histologic diagnosis at CNB warrants further investigation.

In conclusion, CNB was able to reduce unnecessary diagnostic surgery in patients with ATC or TL by virtue of its

Table 3 Comparison of sensitivity, positive predictive value, and diagnostic surgery rates after FNA and CNB in patients with ATC or TL

	ATL		TL		ATL+TL	
	FNA	CNB	FNA	CNB	FNA	CNB
Sensitivity	54.0 (27/50)	76.9 (10/13)	44.8 (13/29)	94.7 (18/19)	50.6 (40/79)	87.5 (28/32)
PPV	87.1 (27/31)	100.0 (10/10)	100.0 (13/13)	100.0 (18/18)	90.9 (40/44)	100.0 (28/28)
Diagnostic surgery*	34.0 (17/50)	23.1 (3/13)	37.9 (11/29)	5.3 (1/19)	35.4 (28/79)	12.5 (4/32)

Note: Data indicate the percentage, with the actual number of patients in parentheses.

FNA fine needle aspiration, *CNB* core needle biopsy, *PPV* positive predictive value

* Diagnostic surgery was defined as that performed when the nodule was initially misdiagnosed as non-ATC or non-TL, but was confirmed as ATC or TL on the subsequent surgery performed for a diagnostic purpose.

superior diagnostic sensitivity and positive predictive value compared to FNA. CNB is thus preferable to FNA for avoiding unnecessary surgery and for proper management in patients with clinically suspected ATC or TL, especially elderly patients with rapidly growing thyroid tumours.

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